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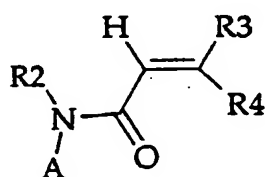
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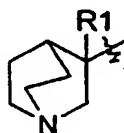
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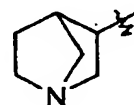
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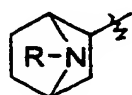
(I)



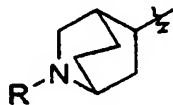
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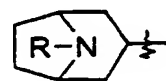
(III)



(IV)



(V)



(VI)

(57) Abstract: A compound of formula (I) wherein A represents (II), (III), (IV), (V) or (VI); R represents hydrogen or methyl; R¹ and R² are independently hydrogen, or C₁-C₄ alkyl; R³ and R⁴ are independently hydrogen, C₁-C₄ alkyl or SAR, provided that at least one of R³ and R⁴ represents SAR; Ar represents a 5- or 6-membered aromatic or heteroaromatic ring containing zero to three nitrogen atoms, zero or one oxygen atom, and zero or one sulfur atom or an 8-, 9- or 10-membered fused aromatic or heteroaromatic ring system containing zero to four nitrogen atoms, zero to one oxygen atom, and zero to one sulfur atom which may optionally be substituted with one or more substituents selected from: hydrogen, halogen, C₁-C₄ alkyl, C₂-C₄ alkenyl, C₂-C₄ alkynyl, aryl, heteroaryl, -CO₂R⁵, -CN, -NO₂, -NR⁶R⁷, -CF₃, -OR⁸; R⁵, R⁶, R⁷, and R⁸ are independently hydrogen, C₁-C₄ alkyl, aryl, heteroaryl, -C(O)R⁹, -C(O)NHR¹⁰, -C(O)R¹¹, -SO₂R¹², or, R⁶ and R⁷ may together be (CH₂)_kQ(CH₂)_k where Q is O, S, NR¹³, or, a bond; j is 2 to 7; k is 0 to 2; R⁹, R¹⁰, R¹¹, R¹², and R¹³, are independently C₁-C₄ alkyl, aryl, or heteroaryl; or an enantiomer thereof, and the pharmaceutically acceptable salts thereof, processes for preparing them, pharmaceutical compositions containing them and their use in therapy, especially in the treatment or prophylaxis of psychotic disorders and intellectual impairment disorders.

WO 01/29034 A1

QUINUCLIDINE ACRYLAMIDES

Technical Field

This invention relates to novel quinuclidine acrylamides or pharmaceutically acceptable salts thereof, processes for preparing them, pharmaceutical compositions containing them and their use in therapy. A further object is to provide active compounds that are potent ligands for nicotinic acetylcholine receptors (nAChRs).

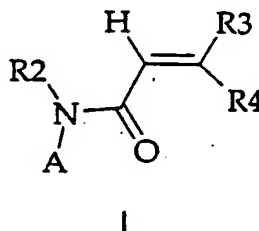
Background of the Invention

The use of compounds which bind nicotinic acetylcholine receptors in the treatment of a range of disorders involving reduced cholinergic function such as Alzheimer's disease, cognitive or attention disorders, anxiety, depression, smoking cessation, neuroprotection, schizophrenia, analgesia, Tourette's syndrome, and Parkinson's disease has been discussed in McDonald et al. (1995) "Nicotinic Acetylcholine Receptors: Molecular Biology, Chemistry and Pharmacology", Chapter 5 in Annual Reports in Medicinal Chemistry, vol. 30, pp. 41-50, Academic Press Inc., San Diego, CA; and in Williams et al. (1994) "Neuronal Nicotinic Acetylcholine Receptors," Drug News & Perspectives, vol. 7, pp. 205-223.

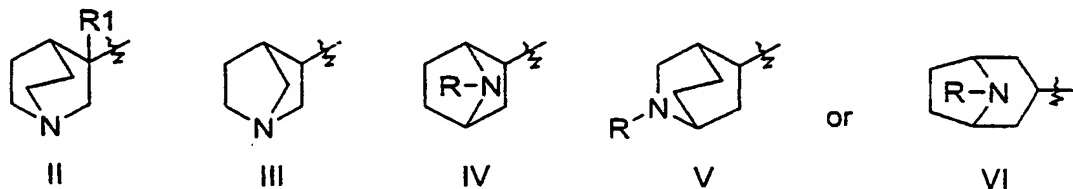
Quinuclidine acrylamide derivatives as potential antitussive agents are known in the art, in EP-A2-581,165. Indole derivatives are known in the art, e.g. in WO94/20465.

Disclosure of the Invention

According to the invention it has been found that compounds of formula I, wherein:



A represents:



R represents hydrogen or methyl;

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R^1 and R^2 are independently hydrogen, or C_1 - C_4 alkyl;

R^3 and R^4 are independently hydrogen, C_1 - C_4 alkyl or SAr , provided that at least one of R^3 and R^4 represents SAr ;

Ar represents a 5- or 6-membered aromatic or heteroaromatic ring containing zero to three nitrogen atoms, zero or one oxygen atom, and zero or one sulfur atom or an 8-, 9- or 10-membered fused aromatic or heteroaromatic ring system containing zero to four nitrogen atoms, zero to one oxygen atom, and zero to one sulfur atom which may optionally be substituted with one or more substituents selected from: hydrogen, halogen, C_1 - C_4 alkyl, C_2 - C_4 alkenyl, C_2 - C_4 alkynyl, aryl, heteroaryl, $-CO_2R^5$, $-CN$, $-NO_2$, $-NR^6R^7$, $-CF_3$, $-OR^8$;

R^5 , R^6 , R^7 , and R^8 are independently hydrogen, C_1 - C_4 alkyl, aryl, heteroaryl, $-C(O)R^9$, $-C(O)NHR^{10}$, $-C(O)R^{11}$, $-SO_2R^{12}$, or,

R^6 and R^7 may together be $(CH_2)_jQ(CH_2)_k$ where Q is O, S, NR^{13} , or, a bond;

j is 2 to 7;

k is 0 to 2;

R^9 , R^{10} , R^{11} , R^{12} , and R^{13} , are independently C_1 - C_4 alkyl, aryl, or heteroaryl;

or an enantiomer thereof, and the pharmaceutically acceptable salts thereof are potent ligands for nicotinic acetylcholine receptors.

Unless otherwise indicated, the C_1 - C_4 alkyl groups referred to herein, e.g., methyl, ethyl, n-propyl, n-butyl, i-propyl, i-butyl, t-butyl, s-butyl, whether alone or part of another group, may be straight-chained or branched, and the C_3 - C_4 alkyl groups may also be cyclic, e.g., cyclopropyl, cyclobutyl.

Unless otherwise indicated, aryl refers to a phenyl ring which may optionally be substituted with one to three of the following substituents chosen from among the following:

halogen, C_1 - C_4 alkyl, C_2 - C_4 alkenyl, C_2 - C_4 alkynyl, CO_2R^7 , $-CN$, $-NO_2$, $-NR^8R^9$, $-CF_3$, $-OR^{10}$.

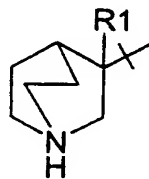
Unless otherwise indicated, heteroaryl refers to a 5- or 6-membered aromatic or heteroaromatic ring containing zero to three nitrogen atoms, zero or one oxygen atom, and zero or one sulfur atom, provided that the ring contains at least one nitrogen, oxygen, or sulfur atom, which may optionally be substituted with one or more substituents chosen from among

the following: halogen, C₁-C₄ alkyl, C₂-C₄ alkenyl, C₂-C₄ alkynyl, CO₂R⁵, -CN, -NO₂, -NR⁶R⁷, -CF₃, -OR⁸.

Unless otherwise indicated, halogen refers to fluorine, chlorine, bromine, or iodine.

Pharmaceutically acceptable derivatives include solvates and salts. For example, the compounds of formula I can form acid addition salts with acids, such as the conventional pharmaceutically acceptable acids, for example, maleic, hydrochloric, hydrobromic, phosphoric, acetic, fumaric, salicylic, citric, lactic, mandelic, tartaric and methanesulfonic acids.

In a preferred embodiment of this aspect of the invention, is compound according to formula I, wherein A represents:



II

or an enantiomer thereof, and the pharmaceutically acceptable salts thereof.

Preferred compounds of the invention include compounds of formula I wherein R¹, R², and one of R³ or R⁴ are hydrogen;

Preferred compounds of the invention further comprise compounds of formula I wherein Ar represents a 5- or 6-membered aromatic or heteroaromatic ring containing zero to three nitrogen atoms, zero or one oxygen atom, and zero or one sulfur atom, including phenyl, 2-pyridyl, or 2-pyrimidinyl, any of which may optionally be substituted with one or more substituents chosen from among the following: hydrogen, halogen, C₁-C₄ alkyl, C₂-C₄ alkenyl, C₂-C₄ alkynyl, -CO₂R⁵, -CN, -NO₂, -NR⁶R⁷, -CF₃, -OR⁸.

Preferred compounds of the invention further comprise compounds of formula I wherein Ar is an heteroaromatic ring.

Preferred compounds of the invention further comprise compounds of formula I wherein Ar is a 6-membered aromatic or heteroaromatic ring, containing zero to two nitrogen atoms.

Preferred compounds of the invention include the following:

N-(1-Aza-bicyclo[2.2.2]oct-3-yl)[Z-3-(phenylthio)propenamide] hydrochloride;

N-(1-Aza-bicyclo[2.2.2]oct-3-yl)[Z-3-(4-methylphenylthio)propenamide];

- N*-(1-Aza-bicyclo[2.2.2]oct-3-yl)[E-3-(4-methylphenylthio)propenamide];
N-(1-Aza-bicyclo[2.2.2]oct-3-yl)[Z-3-(3-methylphenylthio)propenamide];
N-(1-Aza-bicyclo[2.2.2]oct-3-yl)[E-3-(3-methylphenylthio)propenamide];
N-(1-Aza-bicyclo[2.2.2]oct-3-yl)[Z-3-(2-methylphenylthio)propenamide];
5 *N*-(1-Aza-bicyclo[2.2.2]oct-3-yl)[E-3-(2-methylphenylthio)propenamide];
N-(1-Aza-bicyclo[2.2.2]oct-3-yl)[Z-3-(4-methoxyphenylthio)propenamide];
N-(1-Aza-bicyclo[2.2.2]oct-3-yl)[E-3-(4-methoxyphenylthio)propenamide];
N-(1-Aza-bicyclo[2.2.2]oct-3-yl)[Z-3-(3-methoxyphenylthio)propenamide];
N-(1-Aza-bicyclo[2.2.2]oct-3-yl)[E-3-(3-methoxyphenylthio)propenamide];
10 *N*-(1-Aza-bicyclo[2.2.2]oct-3-yl)[Z-3-(2-methoxyphenylthio)propenamide];
N-(1-Aza-bicyclo[2.2.2]oct-3-yl)[E-3-(2-methoxyphenylthio)propenamide];
N-(1-Aza-bicyclo[2.2.2]oct-3-yl)[Z-3-(2-pyridylthio)propenamide];
N-(1-Aza-bicyclo[2.2.2]oct-3-yl)[E-3-(2-pyridylthio)propenamide];
N-(1-Aza-bicyclo[2.2.2]oct-3-yl)[Z-3-(4-pyridylthio)propenamide];
15 *N*-(1-Aza-bicyclo[2.2.2]oct-3-yl)[E-3-(4-pyridylthio)propenamide];
N-(1-Aza-bicyclo[2.2.2]oct-3-yl)[Z-3-(2-pyrimidinylthio)propenamide];
N-(1-Aza-bicyclo[2.2.2]oct-3-yl)[E-3-(2-pyrimidinylthio)propenamide];
N-(1-Aza-bicyclo[2.2.2]oct-3-yl)[Z-3-(2-methyl-3-furanylthio)propenamide];
N-(1-Aza-bicyclo[2.2.2]oct-3-yl)[E-3-(2-methyl-3-furanylthio)propenamide];
20 *N*-(1-Aza-bicyclo[2.2.2]oct-3-yl)[E-3-(2-imidazolylthio)propenamide];
N-(1-Aza-bicyclo[2.2.2]oct-3-yl)[Z-3-(phenylthio)-3-(methyl)propenamide];
N-(1-Aza-bicyclo[2.2.2]oct-3-yl)[Z-3-(2-benzothiazolylthio)propenamide];
N-(1-Aza-bicyclo[2.2.2]oct-3-yl)[E-3-(2-benzothiazolylthio)propenamide];
N-(1-Aza-bicyclo[2.2.2]oct-3-yl)[Z-3-(1-methyl-2-imidazolylthio)propenamide];
25 *N*-(1-Aza-bicyclo[2.2.2]oct-3-yl)[E-3-(1-methyl-2-imidazolylthio)propenamide];
N-(1-Aza-bicyclo[2.2.2]oct-3-yl)[Z-3-(5-methyl-1,3,4-thiadiazol-2-ylthio)propenamide];
N-(1-Aza-bicyclo[2.2.2]oct-3-yl)[E-3-(5-methyl-1,3,4-thiadiazol-2-ylthio)propenamide];
30 *N*-(1-Aza-bicyclo[2.2.2]oct-3-yl)[Z-3-(4-chlorophenylthio)propenamide];
N-(1-Aza-bicyclo[2.2.2]oct-3-yl)[Z-3-(2-thiazolylthio)propenamide];
N-(1-Aza-bicyclo[2.2.2]oct-3-yl)[Z-3-(2-thienylthio)propenamide];

N-(1-Aza-bicyclo[2.2.2]oct-3-yl)[E-3-(2-thienylthio)propenamide];
N-(1-Aza-bicyclo[2.2.2]oct-3-yl)[Z-3-(2-benzoxazolylthio)propenamide];
N-(1-Aza-bicyclo[2.2.2]oct-3-yl)[E-3-(2-benzoxazolylthio)propenamide];
N-(1-Aza-bicyclo[2.2.2]oct-3-yl)[Z-3-(4-trifluoromethyl-2-

5 pyrimidinylthio)propenamide];

N-(1-Aza-bicyclo[2.2.2]oct-3-yl)[Z-3-(4-fluorophenylthio)propenamide];
N-(1-Aza-bicyclo[2.2.2]oct-3-yl)[E-3-(4-fluorophenylthio)propenamide];
N-(1-Aza-bicyclo[2.2.2]oct-3-yl)[Z-3-(2-thiazolo[4,5-b]pyridylthio)propenamide];
(*R*)-*N*-(1-Aza-bicyclo[2.2.2]oct-3-yl)[E-3-(2-thiazolo[4,5-b]pyridylthio)propenamide];
10 *N*-(1-Aza-bicyclo[2.2.2]oct-3-yl)[Z-3-(3-fluorophenylthio)propenamide];
N-(1-Aza-bicyclo[2.2.2]oct-3-yl)[E-3-(3-fluorophenylthio)propenamide];

or an enantiomer thereof, and the pharmaceutically acceptable salts thereof

Particularly preferred compounds of the invention include the following:

(*R*)-*N*-(1-Aza-bicyclo[2.2.2]oct-3-yl)[Z-3-(phenylthio)propenamide] hydrochloride;
15 (*R*)-*N*-(1-Aza-bicyclo[2.2.2]oct-3-yl)[Z-3-(4-methylphenylthio)propenamide];
(*R*)-*N*-(1-Aza-bicyclo[2.2.2]oct-3-yl)[E-3-(4-methylphenylthio)propenamide];
(*R*)-*N*-(1-Aza-bicyclo[2.2.2]oct-3-yl)[Z-3-(3-methylphenylthio)propenamide];
(*R*)-*N*-(1-Aza-bicyclo[2.2.2]oct-3-yl)[E-3-(3-methylphenylthio)propenamide];
(*R*)-*N*-(1-Aza-bicyclo[2.2.2]oct-3-yl)[Z-3-(2-methylphenylthio)propenamide];
20 (*R*)-*N*-(1-Aza-bicyclo[2.2.2]oct-3-yl)[E-3-(2-methylphenylthio)propenamide];
(*R*)-*N*-(1-Aza-bicyclo[2.2.2]oct-3-yl)[Z-3-(4-methoxyphenylthio)propenamide];
(*R*)-*N*-(1-Aza-bicyclo[2.2.2]oct-3-yl)[E-3-(4-methoxyphenylthio)propenamide];
(*R*)-*N*-(1-Aza-bicyclo[2.2.2]oct-3-yl)[Z-3-(3-methoxyphenylthio)propenamide];
(*R*)-*N*-(1-Aza-bicyclo[2.2.2]oct-3-yl)[E-3-(3-methoxyphenylthio)propenamide];
25 (*R*)-*N*-(1-Aza-bicyclo[2.2.2]oct-3-yl)[Z-3-(2-methoxyphenylthio)propenamide];
(*R*)-*N*-(1-Aza-bicyclo[2.2.2]oct-3-yl)[E-3-(2-methoxyphenylthio)propenamide];
(*R*)-*N*-(1-Aza-bicyclo[2.2.2]oct-3-yl)[Z-3-(2-pyridylthio)propenamide];
(*R*)-*N*-(1-Aza-bicyclo[2.2.2]oct-3-yl)[E-3-(2-pyridylthio)propenamide];
(*R*)-*N*-(1-Aza-bicyclo[2.2.2]oct-3-yl)[Z-3-(4-pyridylthio)propenamide];
30 (*R*)-*N*-(1-Aza-bicyclo[2.2.2]oct-3-yl)[E-3-(4-pyridylthio)propenamide];
(*R*)-*N*-(1-Aza-bicyclo[2.2.2]oct-3-yl)[Z-3-(2-pyrimidinylthio)propenamide];
(*R*)-*N*-(1-Aza-bicyclo[2.2.2]oct-3-yl)[E-3-(2-pyrimidinylthio)propenamide];

- (*R*)-*N*-(1-Aza-bicyclo[2.2.2]oct-3-yl)[Z-3-(2-methyl-3-furanylthio)propenamide];
(*R*)-*N*-(1-Aza-bicyclo[2.2.2]oct-3-yl)[E-3-(2-methyl-3-furanylthio)propenamide];
(*R*)-*N*-(1-Aza-bicyclo[2.2.2]oct-3-yl)[E-3-(2-imidazolylthio)propenamide];
(*R*)-*N*-(1-Aza-bicyclo[2.2.2]oct-3-yl)[Z-3-(phenylthio)-3-(methyl)propenamide];
5 (*R*)-*N*-(1-Aza-bicyclo[2.2.2]oct-3-yl)[Z-3-(2-benzothiazolylthio)propenamide];
(*R*)-*N*-(1-Aza-bicyclo[2.2.2]oct-3-yl)[E-3-(2-benzothiazolylthio)propenamide];
(*R*)-*N*-(1-Aza-bicyclo[2.2.2]oct-3-yl)[Z-3-(1-methyl-2-imidazolylthio)propenamide];
(*R*)-*N*-(1-Aza-bicyclo[2.2.2]oct-3-yl)[E-3-(1-methyl-2-imidazolylthio)propenamide];
(*R*)-*N*-(1-Aza-bicyclo[2.2.2]oct-3-yl)[Z-3-(5-methyl-1,3,4-thiadiazol-2-
10 ylthio)propenamide];
(*R*)-*N*-(1-Aza-bicyclo[2.2.2]oct-3-yl)[E-3-(5-methyl-1,3,4-thiadiazol-2-
ylthio)propenamide];
(*R*)-*N*-(1-Aza-bicyclo[2.2.2]oct-3-yl)[Z-3-(4-chlorophenylthio)propenamide];
(*R*)-*N*-(1-Aza-bicyclo[2.2.2]oct-3-yl)[Z-3-(2-thiazolylthio)propenamide];
15 (*R*)-*N*-(1-Aza-bicyclo[2.2.2]oct-3-yl)[Z-3-(2-thienylthio)propenamide];
(*R*)-*N*-(1-Aza-bicyclo[2.2.2]oct-3-yl)[E-3-(2-thienylthio)propenamide];
(*R*)-*N*-(1-Aza-bicyclo[2.2.2]oct-3-yl)[Z-3-(2-benzoxazolylthio)propenamide];
(*R*)-*N*-(1-Aza-bicyclo[2.2.2]oct-3-yl)[E-3-(2-benzoxazolylthio)propenamide];
(*R*)-*N*-(1-Aza-bicyclo[2.2.2]oct-3-yl)[Z-3-(4-trifluoromethyl-2-
20 pyrimidinylthio)propenamide];
(*R*)-*N*-(1-Aza-bicyclo[2.2.2]oct-3-yl)[Z-3-(4-fluorophenylthio)propenamide];
(*R*)-*N*-(1-Aza-bicyclo[2.2.2]oct-3-yl)[E-3-(4-fluorophenylthio)propenamide];
(*R*)-*N*-(1-Aza-bicyclo[2.2.2]oct-3-yl)[Z-3-(2-thiazolo[4,5-b]pyridylthio)propenamide];
(*R*)-*N*-(1-Aza-bicyclo[2.2.2]oct-3-yl)[E-3-(2-thiazolo[4,5-b]pyridylthio)propenamide];
25 (*R*)-*N*-(1-Aza-bicyclo[2.2.2]oct-3-yl)[Z-3-(3-fluorophenylthio)propenamide];
(*R*)-*N*-(1-Aza-bicyclo[2.2.2]oct-3-yl)[E-3-(3-fluorophenylthio)propenamide];

or an enantiomer thereof, and the pharmaceutically acceptable salts thereof.

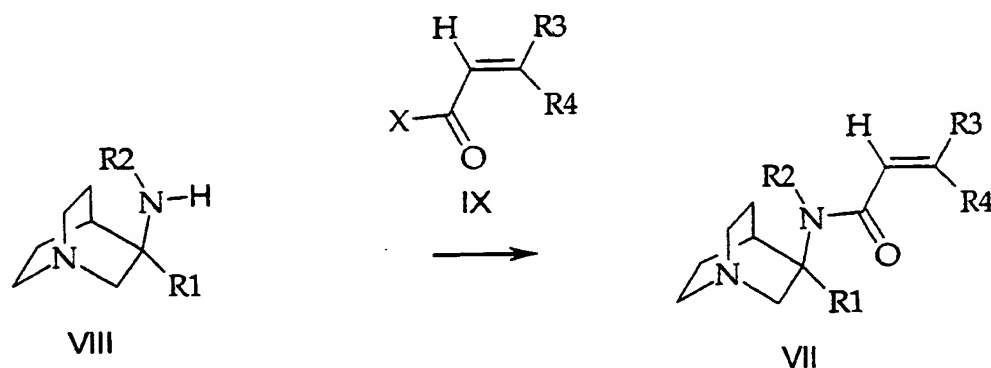
Further particularly preferred compounds of the invention includes:

- (*R*)-*N*-(1-Aza-bicyclo[2.2.2]oct-3-yl)[Z-3-(2-pyridylthio)propenamide];
30 (*R*)-*N*-(1-Aza-bicyclo[2.2.2]oct-3-yl)[E-3-(2-pyridylthio)propenamide];
(*R*)-*N*-(1-Aza-bicyclo[2.2.2]oct-3-yl)[Z-3-(2-pyrimidinylthio)propenamide];

or an enantiomer thereof, and the pharmaceutically acceptable salts thereof.

Methods of Preparation

In the reaction schemes and text that follow, R^1 , R^2 , R^3 and R^4 , unless otherwise indicated, are as defined above for formula VII. The compounds of formula VII may be prepared according to the methods outlined in Scheme 1.

**Scheme 1**

10

Compounds of formula I may be prepared from compounds of formula II by reaction with a compound of formula III, wherein X represents a suitable leaving group, using a suitable acylation procedure.

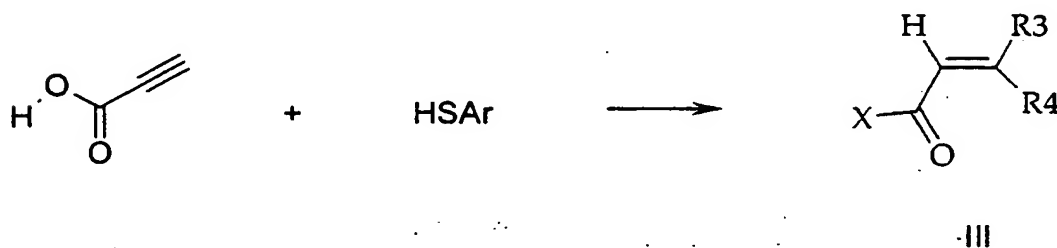
Suitable leaving groups X include: OH, halogen, OAlkyl, OAr, OCOAlkyl, OCOAr, azide. A suitable acylation procedure involves treatment of a compound of formula II with a compound of formula III at 0-120 °C in a suitable solvent. The presence of a base, or, when X=OH, a coupling agent, may also be necessary for the reaction to occur. Suitable bases for the reaction include: 4-(*N,N*-dimethylamino)pyridine, pyridine, triethylamine, *N,N*-diisopropylethylamine. The preferred base is *N,N*-diisopropylethylamine. Suitable coupling agents when X=OH include: carbodiimides, for example 1,3-dicyclohexylcarbodiimide or 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride; phosphonium reagents, for example benzotriazol-1-yloxytris(dimethylamino)phosphonium hexafluorophosphate or benzotriazol-1-yloxytripyrrolidinophosphonium hexafluorophosphate; and uronium reagents, for example O-benzotriazol-1-yl-*N,N,N',N'*-tetramethyluronium tetrafluoroborate. The preferred coupling agent is O-benzotriazol-1-yl-*N,N,N',N'*-tetramethyluronium tetrafluoroborate. Suitable solvents for the reaction include *N,N*-dimethylformamide,

dimethylsulfoxide, tetrahydrofuran, or chloroform. The preferred solvent is *N,N*-dimethylformamide. The reaction is preferably performed at a temperature of 0-50 °C, and most preferably at a temperature of 20-30 °C.

Compounds of formula II in which R² represents an alkyl group may be prepared from
5 compounds of formula II in which R² represents hydrogen by a suitable alkylation procedure.

Typical alkylation procedures include treatment with an appropriate alkyl halide or sulfonate ester and base, for example sodium hydride, in a suitable solvent, for example DMF, or reductive alkylation using the appropriate aldehyde or ketone together with a suitable
10 reducing agent in an inert solvent. The preferred method is reductive alkylation. Suitable reducing agents include sodium borohydride and sodium cyanoborohydride. The preferred reducing agent is sodium borohydride. Suitable inert solvents include water, methanol or ethanol. The preferred solvent is methanol. The reaction is usually conducted at a temperature of 0 °C to 100 °C, preferably from 20 °C to 65 °C.

Compounds of formula II and III are either commercially available, or may be
15 prepared by methods known to one skilled in the art. For example compound III may be prepared as shown in Scheme 2 according to the method described by G. Joshi, et al., Chemistry and Industry, (1991), 281.



20 **Scheme 2**

Use of compounds II and III as intermediates in a synthesis of a ligand for nicotinic acetylcholine receptors is another aspect of the invention.

Where necessary, hydroxy, amino, or other reactive groups may be protected using a
25 protecting group as described in the standard text "Protecting groups in Organic Synthesis", 3rd Edition (1999) by Greene and Wuts.

The above described reactions, unless otherwise noted, are usually conducted at a pressure of about one to about three atmospheres, preferably at ambient pressure (about one

atmosphere). Unless otherwise stated, the above-described reactions are conducted under an inert atmosphere, preferably under a nitrogen atmosphere.

The compounds of the invention and intermediates may be isolated from their reaction mixtures by standard techniques.

- 5 Acid addition salts of the compounds of formula I which may be mentioned include salts of mineral acids, for example the hydrochloride and hydrobromide salts; and salts formed with organic acids such as formate, acetate, maleate, benzoate, tartrate, and fumarate salts.

- 10 Acid addition salts of compounds of formula I may be formed by reacting the free base or a salt, enantiomer or protected derivative thereof, with one or more equivalents of the appropriate acid. The reaction may be carried out in a solvent or medium in which the salt is insoluble or in a solvent in which the salt is soluble, e.g., water, dioxane, ethanol, tetrahydrofuran or diethyl ether, or a mixture of solvents, which may be removed in vacuum or by freeze drying. The reaction may be a metathetical process or it may be carried out on an ion
15 exchange resin.

- The compounds of formula I exist in tautomeric or enantiomeric forms, all of which are included within the scope of the invention. The various optical isomers may be isolated by separation of a racemic mixture of the compounds using conventional techniques, e.g. fractional crystallization, or chiral HPLC. Alternatively the individual enantiomers may be
20 made by reaction of the appropriate optically active starting materials under reaction conditions which will not cause racemization.

Pharmaceutical Compositions

- A further aspect of the invention relates to a pharmaceutical composition for treating or preventing a condition or disorder as exemplified below arising from dysfunction of
25 nicotinic acetylcholine receptor neurotransmission in a mammal, preferably a human, comprising an amount of a compound of formula I, an enantiomer thereof and/or a pharmaceutically acceptable salt thereof, effective in treating or preventing such disorder or condition and an inert pharmaceutically acceptable carrier.

- For the above-mentioned uses the dosage administered will, of course, vary with the
30 compound employed, the mode of administration and the treatment desired. However, in general, satisfactory results will be obtained when the compounds of the invention are administered at a daily dosage of from about 0.1 mg to about 20 mg per kg of mammalian

body weight, preferably given in divided doses 1 to 4 times a day or in sustained release form. For man, the total daily dose is in the range of from 5 mg to 1,400 mg, more preferably from 10 mg to 100 mg, and unit dosage forms suitable for oral administration comprise from 2 mg to 1,400 mg of the compound admixed with a solid or liquid pharmaceutical carrier or diluent.

5 The compounds of formula I or an enantiomer thereof and/or pharmaceutically acceptable salts thereof, may be used on their own or in the form of appropriate medicinal preparations for enteral, parenteral, oral, rectal or nasal administration. According to a further aspect of the invention, there is provided a pharmaceutical composition preferably comprising less than 80% and more preferably less than 50% by weight of a compound of the invention in
10 admixture with an inert pharmaceutically acceptable diluent or carrier.

Examples of suitable diluents and carriers are:

- for tablets and dragees: lactose, starch, talc, stearic acid; for capsules: tartaric acid or lactose;
- for injectable solutions: water, alcohols, glycerin, vegetable oils; for suppositories: natural
15 or hardened oils or waxes.

There is also provided a process for the preparation of such a pharmaceutical composition which comprises mixing the ingredients simultaneously or sequentially.

Utility

A further aspect of the invention is the use of a compound according to the invention,
20 an enantiomer thereof or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for the treatment or prophylaxis of one of the below mentioned diseases or conditions; and a method of treatment or prophylaxis of one of the below mentioned diseases or conditions, which comprises administering a therapeutically effective amount of a compound according to the invention, or an enantiomer thereof or a pharmaceutically
25 acceptable salt thereof, to a patient.

Compounds according to the invention are agonists of nicotinic acetylcholine receptors. While not being limited by theory, it is believed that agonists of the $\alpha 7$ nAChR (nicotinic acetylcholine receptor) subtype should be useful in the treatment or prophylaxis of psychotic disorders and intellectual impairment disorders, and have advantages over
30 compounds which are or are also agonists of the $\alpha 4$ nAChR subtype. Therefore, compounds which are selective for the $\alpha 7$ nAChR subtype are preferred. The compounds of the invention are selective for the $\alpha 7$ nAChR subtype. The compounds of the invention are intended as

pharmaceuticals, in particular in the treatment or prophylaxis of psychotic disorders and intellectual impairment disorders. Examples of psychotic disorders include schizophrenia, mania and manic depression, and anxiety. Examples of intellectual impairment disorders include Alzheimer's disease, learning deficit, cognition deficit, attention deficit, memory loss, 5 Lewy Body Dementia, and Attention Deficit Hyperactivity Disorder. The compounds of the invention may also be useful as analgesics in the treatment of pain (including chronic pain) and in the treatment or prophylaxis of Parkinson's disease, Huntington's disease, Tourette's syndrome, and neurodegenerative disorders in which there is loss of cholinergic synapses. The compounds may further be indicated for the treatment or prophylaxis of jetlag, for use in 10 inducing the cessation of smoking, and for the treatment or prophylaxis of nicotine addiction (including that resulting from exposure to products containing nicotine).

It is also believed that compounds according to the invention are useful in the treatment and prophylaxis of ulcerative colitis.

Pharmacology

15 The pharmacological activity of the compounds of the invention may be measured in the tests set out below:

Test A - Assay for affinity at $\alpha 7$ nAChR subtype

125 I- α -Bungarotoxin (BTX) binding to rat hippocampal membranes. Rat hippocampi were homogenized in 20 volumes of cold homogenization buffer (HB: concentrations of 20 constituents (mM): tris(hydroxymethyl)aminomethane 50; MgCl_2 1; NaCl 120; KCl 5; pH 7.4). The homogenate was centrifuged for 5 minutes at 1000 g, the supernatant was saved and the pellet re-extracted. The pooled supernatants were centrifuged for 20 minutes at 12,000 x g, washed, and resuspended in HB. Membranes (30–80 μg) were incubated with 5 nM [125 I] α -BTX, 1 mg/mL BSA (bovine serum albumin), test drug, and either 2 mM CaCl_2 or 0.5 mM 25 EGTA [ethylene glycol-bis(β -aminoethylether)] for 2 hours at 21 °C, and then filtered and washed 4 times over Whatman glass fibre filters (thickness C) using a Brandel cell harvester. Pretreating the filters for 3 hours with 1% (BSA/0.01% PEI (polyethyleneimine)) in water was critical for low filter blanks (0.07% of total counts per minute). Nonspecific binding was described by 100 μM (–)-nicotine, and specific binding was typically 75%.

30 **Test B - Assay for affinity to the $\alpha 4$ nAChR subtype**

[³H]-(-)-nicotine binding. Using a procedure modified from Martino-Barrows and Kellar (Mol Pharm (1987) 31:169-174), rat brain (cortex and hippocampus) was homogenized as in the [¹²⁵I]-α-BTX binding assay, centrifuged for 20 minutes at 12,000 x g, washed twice, and then resuspended in HB containing 100 μM diisopropyl fluorophosphate. After 20 minutes at 4 °C, membranes (approximately 0.5 mg) were incubated with 3 nM [³H]-(-)-nicotine, test drug, 1 μM atropine, and either 2 mM CaCl₂ or 0.5 mM EGTA for 1 hour at 4 °C, and then filtered over Whatman glass fibre filters (thickness C) (pretreated for 1 hour with 0.5% PEI) using a Brandel cell harvester. Nonspecific binding was described by 100 μM carbachol, and specific binding was typically 84%.

10 Binding data analysis for Tests A and B

IC₅₀ values and pseudo Hill coefficients (n_H) were calculated using the non-linear curve fitting program ALLFIT (DeLean A, Munson P J and Rodbard D (1977) Am. J. Physiol., 235:E97-E102). Saturation curves were fitted to a one site model, using the non-linear regression program ENZFITTER (Leatherbarrow, R.J. (1987)), yielding K_D values of 15 1.67 and 1.70 nM for the ¹²⁵I-α-BTX and [³H]-(-)-nicotine ligands respectively. K_i values were estimated using the general Cheng-Prusoff equation:

$$K_i = [IC_{50}] / ((2 + ([ligand]/K_D)^n)^{1/n} - 1)$$

where a value of n=1 was used whenever n_H<1.5 and a value of n=2 was used when n_H≥1.5.

Samples were assayed in triplicate and were typically ±5%. K_i values were determined using 20 6 or more drug concentrations. The compounds of the invention are compounds with binding affinities (K_i) of less than 1000 nM in either Test A or Test B, indicating that they are expected to have useful therapeutic activity.

General Experimental Procedures

Commercial reagents were used without further purification. Mass spectra were 25 recorded using either a Hewlett Packard 5988A or a MicroMass Quattro-1 Mass Spectrometer and are reported as m/z for the parent molecular ion. Room temperature refers to 20–25°C.

Examples

The following examples are preferred non-limiting examples embodying preferred aspects of the invention.

30 Example 1

(R)-N-(1-Aza-bicyclo[2.2.2]oct-3-yl)[Z-3-(phenylthio)propenamide] hydrochloride

To a stirred solution of (R)-1-Aza-bicyclo[2.2.2]oct-3-ylamine dihydrochloride (25 g, 0.125 mol), 3-(phenylthio)acrylic acid (23.5 g, 0.13 mol), and diisopropylethylamine (90 ml) in dry DMF (600 ml) at ambient temperature was added in succession 1-hydroxybenzotriazole
5 hydrate (17 g, 0.126 mol) and O-benzotriazol-1-yl-N,N,N',N'-tetramethyluronium tetrafluoroborate (40 g, 0.124 mol). The resulting amber-colored solution was stirred overnight, diluted with water (1 vol), and extracted with ether (2x700 ml). The aqueous phase was made basic (pH 10) with 50% aqueous sodium hydroxide and extracted with chloroform (3x700 ml). The chloroform extracts were combined, washed with water, brine, dried over
10 sodium sulfate and concentrated to dryness to give crude product as a syrup (40 g). The syrup was taken in isopropanol (1L), made acidic with gaseous HCL, and allowed to stand. The resulting solid was collected by filtration, recrystallized from isopropanol (2x), and dried in vacuo to give the title compound (8 g) as a white solid. MS (ES⁺) 289. (MH⁺).

Purification of the mother liquors from above by chromatography on silica gel using
15 ammoniated methanol/chloroform mixtures as the eluent gave (R)-N-(1-Aza-bicyclo[2.2.2]oct-3-yl)[E-3-(phenylthio)propenamide]; MS (ES⁺) 289. (MH⁺).

Example 2

(R)-N-(1-Aza-bicyclo[2.2.2]oct-3-yl)[Z-3-(4-methylphenylthio)propenamide] and
(R)-N-(1-Aza-bicyclo[2.2.2]oct-3-yl)[E-3-(4-methylphenylthio)propenamide]

20 Employing essentially the same procedure as that described in Example 1 above but substituting 3-(4-methylphenylthio)acrylic acid for the 3-(phenylthio)acrylic acid and purifying by chromatography on silica gel using ammoniated methanol/chloroform mixtures as the eluent resulted in formation of the title compounds; MS (ES⁺) 303. (MH⁺).

Example 3

25 (R)-N-(1-Aza-bicyclo[2.2.2]oct-3-yl)[Z-3-(3-methylphenylthio)propenamide] and
(R)-N-(1-Aza-bicyclo[2.2.2]oct-3-yl)[E-3-(3-methylphenylthio)propenamide]

Employing essentially the same procedure as that described in Example 1 above but substituting 3-(3-methylphenylthio)acrylic acid for the 3-(phenylthio)acrylic acid and purifying by chromatography on silica gel using ammoniated methanol/chloroform mixtures
30 as the eluent resulted in formation of the title compounds; MS (ES⁺) 303. (MH⁺).

Example 4

(R)-N-(1-Aza-bicyclo[2.2.2]oct-3-yl)[Z-3-(2-methylphenylthio)propenamide] and

(R)-N-(1-Aza-bicyclo[2.2.2]oct-3-yl)[E-3-(2-methylphenylthio)propenamide]

Employing essentially the same procedure as that described in Example 1 above but substituting 3-(2-methylphenylthio)acrylic acid for the 3-(phenylthio)acrylic acid and purifying by chromatography on silica gel using ammoniated methanol/chloroform mixtures as the eluent resulted in formation of the title compounds; MS (ES⁺) 303. (MH⁺).

Example 5

(R)-N-(1-Aza-bicyclo[2.2.2]oct-3-yl)[Z-3-(4-methoxyphenylthio)propenamide] and

(R)-N-(1-Aza-bicyclo[2.2.2]oct-3-yl)[E-3-(4-methoxyphenylthio)propenamide]

Employing essentially the same procedure as that described in Example 1 above but substituting 3-(4-methoxyphenylthio)acrylic acid for the 3-(phenylthio)acrylic acid and purifying by chromatography on silica gel using ammoniated methanol/chloroform mixtures as the eluent resulted in formation of the title compounds; MS (ES⁺) 319. (MH⁺).

Example 6

(R)-N-(1-Aza-bicyclo[2.2.2]oct-3-yl)[Z-3-(3-methoxyphenylthio)propenamide] and

(R)-N-(1-Aza-bicyclo[2.2.2]oct-3-yl)[E-3-(3-methoxyphenylthio)propenamide]

Employing essentially the same procedure as that described in Example 1 above but substituting 3-(3-methoxyphenylthio)acrylic acid for the 3-(phenylthio)acrylic acid and purifying by chromatography on silica gel using ammoniated methanol/chloroform mixtures as the eluent resulted in formation of the title compounds; MS (ES⁺) 319. (MH⁺).

Example 7

(R)-N-(1-Aza-bicyclo[2.2.2]oct-3-yl)[Z-3-(2-methoxyphenylthio)propenamide] and

(R)-N-(1-Aza-bicyclo[2.2.2]oct-3-yl)[E-3-(2-methoxyphenylthio)propenamide]

Employing essentially the same procedure as that described in Example 1 above but substituting 3-(2-methoxyphenylthio)acrylic acid for the 3-(phenylthio)acrylic acid and purifying by chromatography on silica gel using ammoniated methanol/chloroform mixtures as the eluent resulted in formation of the title compounds; MS (ES⁺) 319. (MH⁺).

Example 8

(R)-N-(1-Aza-bicyclo[2.2.2]oct-3-yl)[Z-3-(2-pyridylthio)propenamide] and

(R)-N-(1-Aza-bicyclo[2.2.2]oct-3-yl)[E-3-(2-pyridylthio)propenamide]

Employing essentially the same procedure as that described in Example 1 above but substituting 3-(2-pyridylthio)acrylic acid for the 3-(phenylthio)acrylic acid and purifying by

chromatography on silica gel using ammoniated methanol/chloroform mixtures as the eluent resulted in formation of the title compounds; MS (ES⁺) 290. (MH⁺).

Example 9

(R)-N-(1-Aza-bicyclo[2.2.2]oct-3-yl)[Z-3-(4-pyridylthio)propenamide] and

5 (R)-N-(1-Aza-bicyclo[2.2.2]oct-3-yl)[E-3-(4-pyridylthio)propenamide]

Employing essentially the same procedure as that described in Example 1 above but substituting 3-(4-pyridylthio)acrylic acid for the 3-(phenylthio)acrylic acid and purifying by chromatography on silica gel using ammoniated methanol/chloroform mixtures as the eluent resulted in formation of the title compounds; MS (ES⁺) 290. (MH⁺).

10 **Example 10**

(R)-N-(1-Aza-bicyclo[2.2.2]oct-3-yl)[Z-3-(2-pyrimidinylthio)propenamide] and

(R)-N-(1-Aza-bicyclo[2.2.2]oct-3-yl)[E-3-(2-pyrimidinylthio)propenamide]

Employing essentially the same procedure as that described in Example 1 above but substituting 3-(2-pyrimidinylthio)acrylic acid for the 3-(phenylthio)acrylic acid and purifying
15 by chromatography on silica gel using ammoniated methanol/chloroform mixtures as the eluent resulted in formation of the title compounds; MS (ES⁺) 291. (MH⁺).

Example 11

(R)-N-(1-Aza-bicyclo[2.2.2]oct-3-yl)[Z-3-(2-methyl-3-furanylthio)propenamide] and

(R)-N-(1-Aza-bicyclo[2.2.2]oct-3-yl)[E-3-(2-methyl-3-furanylthio)propenamide]

20 Employing essentially the same procedure as that described in Example 1 above but substituting 3-(2-methyl-3-furanylthio)acrylic acid for the 3-(phenylthio)acrylic acid and purifying by chromatography on silica gel using ammoniated methanol/chloroform mixtures as the eluent resulted in formation of the title compounds; MS (ES⁺) 293. (MH⁺).

Example 12

25 (R)-N-(1-Aza-bicyclo[2.2.2]oct-3-yl)[E-3-(2-imidazolylthio)propenamide]

Employing essentially the same procedure as that described in Example 1 above but substituting 3-(2-imidazolylthio)acrylic acid for the 3-(phenylthio)acrylic acid and purifying by chromatography on silica gel using ammoniated methanol/chloroform mixtures as the eluent resulted in formation of the title compound; MS (ES⁺) 279. (MH⁺).

30 **Example 13**

(R)-N-(1-Aza-bicyclo[2.2.2]oct-3-yl)[Z-3-(phenylthio)-3-(methyl)propenamide]

Employing essentially the same procedure as that described in Example 1 above but substituting 3-(phenylthio)-3-methylacrylic acid for the 3-(phenylthio)acrylic acid and purifying by chromatography on silica gel using ammoniated methanol/chloroform mixtures as the eluent resulted in formation of the title compound; MS (ES⁺) 303. (MH⁺).

5 **Example 14**

(R)-N-(1-Aza-bicyclo[2.2.2]oct-3-yl)[Z-3-(2-benzothiazolylthio)propenamide] and
(R)-N-(1-Aza-bicyclo[2.2.2]oct-3-yl)[E-3-(2-benzothiazolylthio)propenamide]

Employing essentially the same procedure as that described in Example 1 above but substituting 3-(2-benzothiazolylthio)acrylic acid for the 3-(phenylthio)acrylic acid and
10 purifying by chromatography on silica gel using ammoniated methanol/chloroform mixtures as the eluent resulted in formation of the title compounds; MS (ES⁺) 346. (MH⁺).

Example 15

(R)-N-(1-Aza-bicyclo[2.2.2]oct-3-yl)[Z-3-(1-methyl-2-imidazolylthio)propenamide] and (R)-N-(1-Aza-bicyclo[2.2.2]oct-3-yl)[E-3-(1-methyl-2-imidazolylthio)propenamide]

15 Employing essentially the same procedure as that described in Example 1 above but substituting 3-(1-methyl-2-imidazolylthio)acrylic acid for the 3-(phenylthio)acrylic acid and purifying by chromatography on silica gel using ammoniated methanol/chloroform mixtures as the eluent resulted in formation of the title compounds; MS (ES⁺) 293. (MH⁺).

Example 16

20 (R)-N-(1-Aza-bicyclo[2.2.2]oct-3-yl)[Z-3-(5-methyl-1,3,4-thiadiazol-2-ylthio)propenamide]
and

(R)-N-(1-Aza-bicyclo[2.2.2]oct-3-yl)[E-3-(5-methyl-1,3,4-thiadiazol-2-ylthio)propenamide]

Employing essentially the same procedure as that described in Example 1 above but substituting 3-(5-methyl-1,3,4-thiadiazol-2-ylthio)acrylic acid for the 3-(phenylthio)acrylic
25 acid and purifying by chromatography on silica gel using ammoniated methanol/chloroform mixtures as the eluent resulted in formation of the title compounds; MS (ES⁺) 311. (MH⁺).

Example 17

(R)-N-(1-Aza-bicyclo[2.2.2]oct-3-yl)[Z-3-(4-chlorophenylthio)propenamide]

Employing essentially the same procedure as that described in Example 1 above but
30 substituting 3-(4-chlorophenylthio)acrylic acid for the 3-(phenylthio)acrylic acid and purifying by chromatography on silica gel using ammoniated methanol/chloroform mixtures as the eluent resulted in formation of the title compound; MS (ES⁺) 324,326. (MH⁺).

Example 18

(R)-N-(1-Aza-bicyclo[2.2.2]oct-3-yl)[Z-3-(2-thiazolylthio)propenamide]

Employing essentially the same procedure as that described in Example 1 above but substituting 3-(2-thiazolylthio)acrylic acid for the 3-(phenylthio)acrylic acid and purifying by chromatography on silica gel using ammoniated methanol/chloroform mixtures as the eluent resulted in formation of the title compound; MS (ES+) 296. (MH+).

Example 19

(R)-N-(1-Aza-bicyclo[2.2.2]oct-3-yl)[Z-3-(2-thienylthio)propenamide] and

(R)-N-(1-Aza-bicyclo[2.2.2]oct-3-yl)[E-3-(2-thienylthio)propenamide]

Employing essentially the same procedure as that described in Example 1 above but substituting 3-(2-thienylthio)acrylic acid for the 3-(phenylthio)acrylic acid and purifying by chromatography on silica gel using ammoniated methanol/chloroform mixtures as the eluent resulted in formation of the title compounds; MS (ES+) 295. (MH+).

Example 20

(R)-N-(1-Aza-bicyclo[2.2.2]oct-3-yl)[Z-3-(2-benzoxazolylthio)propenamide] and

(R)-N-(1-Aza-bicyclo[2.2.2]oct-3-yl)[E-3-(2-benzoxazolylthio)propenamide]

Employing essentially the same procedure as that described in Example 1 above but substituting 3-(2-benzoxazolylthio)acrylic acid for the 3-(phenylthio)acrylic acid and purifying by chromatography on silica gel using ammoniated methanol/chloroform mixtures as the eluent resulted in formation of the title compounds; MS (ES+) 330. (MH+).

Example 21

(R)-N-(1-Aza-bicyclo[2.2.2]oct-3-yl)[Z-3-(4-trifluoromethyl-2-pyrimidinylthio)propenamide]

Employing essentially the same procedure as that described in Example 1 above but substituting 3-(4-trifluoromethyl-2-pyrimidinylthio)acrylic acid for the 3-(phenylthio)acrylic acid and purifying by chromatography on silica gel using ammoniated methanol/chloroform mixtures as the eluent resulted in formation of the title compound; MS (ES+) 359. (MH+).

Example 22

(R)-N-(1-Aza-bicyclo[2.2.2]oct-3-yl)[Z-3-(4-fluorophenylthio)propenamide] and

(R)-N-(1-Aza-bicyclo[2.2.2]oct-3-yl)[E-3-(4-fluorophenylthio)propenamide]

Employing essentially the same procedure as that described in Example 1 above but substituting 3-(4-fluorophenylthio)acrylic acid for the 3-(phenylthio)acrylic acid and purifying

by chromatography on silica gel using ammoniated methanol/chloroform mixtures as the eluent resulted in formation of the title compounds; MS (ES+) 307. (MH+).

Example 23

- 5 (R)-N-(1-Aza-bicyclo[2.2.2]oct-3-yl)[Z-3-(2-thiazolo[4,5-b]pyridylthio)propenamide] and
(R)-N-(1-Aza-bicyclo[2.2.2]oct-3-yl)[E-3-(2-thiazolo[4,5-b]pyridylthio)propenamide]

Employing essentially the same procedure as that described in Example 1 above but substituting 3-(2-thiazolo[4,5-b]pyridylthio)acrylic acid for the 3-(phenylthio)acrylic acid and purifying by chromatography on silica gel using ammoniated methanol/chloroform mixtures as the eluent resulted in formation of the title compounds; MS (ES+) 347. (MH+).

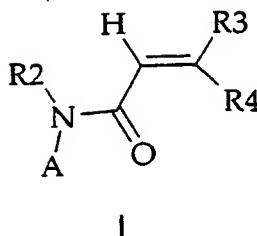
10 **Example 24**

- (R)-N-(1-Aza-bicyclo[2.2.2]oct-3-yl)[Z-3-(3-fluorophenylthio)propenamide] and
(R)-N-(1-Aza-bicyclo[2.2.2]oct-3-yl)[E-3-(3-fluorophenylthio)propenamide]

- Employing essentially the same procedure as that described in Example 1 above but substituting 3-(3-fluorophenylthio)acrylic acid for the 3-(phenylthio)acrylic acid and purifying
15 by chromatography on silica gel using ammoniated methanol/chloroform mixtures as the eluent resulted in formation of the title compounds; MS (ES+) 307. (MH+).

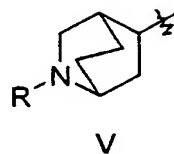
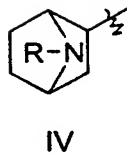
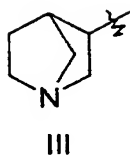
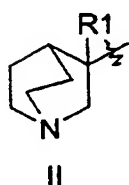
CLAIMS

1. A compound of formula I,

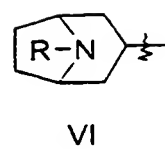


- 5 wherein:

A represents:



or



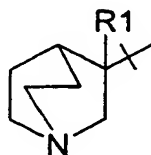
- 10 R represents hydrogen or methyl;
 R¹ and R² are independently hydrogen, or C₁-C₄ alkyl;
 R³ and R⁴ are independently hydrogen, C₁-C₄ alkyl or SAr, provided that at least one of
 R³ and R⁴ represents SAr;
 Ar represents a 5- or 6-membered aromatic or heteroaromatic ring containing zero to
 15 three nitrogen atoms, zero or one oxygen atom, and zero or one sulfur atom or an 8-, 9-
 or 10-membered fused aromatic or heteroaromatic ring system containing zero to four
 nitrogen atoms, zero to one oxygen atom, and zero to one sulfur atom which may
 optionally be substituted with one or more substituents selected from: hydrogen,
 halogen, C₁-C₄ alkyl, C₂-C₄ alkenyl, C₂-C₄ alkynyl, aryl, heteroaryl, -CO₂R⁵, -CN, -
 20 NO₂, -NR⁶R⁷, -CF₃, -OR⁸;
 R⁵, R⁶, R⁷, and R⁸ are independently hydrogen, C₁-C₄ alkyl, aryl, heteroaryl.
 -C(O)R⁹, -C(O)NHR¹⁰, -C(O)R¹¹, -SO₂R¹²; or,
 R⁶ and R⁷ may together be (CH₂)_jQ(CH₂)_k where Q is O, S, NR¹³, or,
 a bond;
 25 j is 2 to 7;

k is 0 to 2;

R^9 , R^{10} , R^{11} , R^{12} , and R^{13} , are independently C_1 - C_4 alkyl, aryl, or heteroaryl; or an enantiomer thereof, and the pharmaceutically acceptable salts thereof.

2. A compound according to claim 1, wherein:

A represents:



II

or an enantiomer thereof, and the pharmaceutically acceptable salts thereof.

3. A compound according to claim 1, wherein R^1 , R^2 , and one of R^3 , R^4 are hydrogen.

4. A compound according to claim 1, wherein Ar is a 5- or 6-membered aromatic or heteroaromatic ring containing zero to three nitrogen atoms, zero or one oxygen atom, and zero or one sulfur atom, including phenyl, 2-pyridyl, or 2-pyrimidinyl, any of which may optionally be substituted with one or more substituents selected from: hydrogen, halogen, C_1 - C_4 alkyl, C_2 - C_4 alkenyl, C_2 - C_4 alkynyl, $-CO_2R^5$, $-CN$, $-NO_2$, $-NR^6R^7$, $-CF_3$, $-OR^8$.

5. A compound according to claim 4, wherein Ar is an heteroaromatic ring.

6. A compound according to claim 4, wherein Ar is a 6-membered aromatic or heteroaromatic ring containing zero to two nitrogen atoms.

7. A compound according to claim 1, said compound being:

N-(1-Aza-bicyclo[2.2.2]oct-3-yl)[Z-3-(phenylthio)propenamide] hydrochloride;
N-(1-Aza-bicyclo[2.2.2]oct-3-yl)[Z-3-(4-methylphenylthio)propenamide];
N-(1-Aza-bicyclo[2.2.2]oct-3-yl)[E-3-(4-methylphenylthio)propenamide];
N-(1-Aza-bicyclo[2.2.2]oct-3-yl)[Z-3-(3-methylphenylthio)propenamide];
N-(1-Aza-bicyclo[2.2.2]oct-3-yl)[E-3-(3-methylphenylthio)propenamide];

- N*-(1-Aza-bicyclo[2.2.2]oct-3-yl)[Z-3-(2-methylphenylthio)propenamide];
N-(1-Aza-bicyclo[2.2.2]oct-3-yl)[E-3-(2-methylphenylthio)propenamide];
N-(1-Aza-bicyclo[2.2.2]oct-3-yl)[Z-3-(4-methoxyphenylthio)propenamide];
N-(1-Aza-bicyclo[2.2.2]oct-3-yl)[E-3-(4-methoxyphenylthio)propenamide];
5 *N*-(1-Aza-bicyclo[2.2.2]oct-3-yl)[Z-3-(3-methoxyphenylthio)propenamide];
N-(1-Aza-bicyclo[2.2.2]oct-3-yl)[E-3-(3-methoxyphenylthio)propenamide];
N-(1-Aza-bicyclo[2.2.2]oct-3-yl)[Z-3-(2-methoxyphenylthio)propenamide];
N-(1-Aza-bicyclo[2.2.2]oct-3-yl)[E-3-(2-methoxyphenylthio)propenamide];
N-(1-Aza-bicyclo[2.2.2]oct-3-yl)[Z-3-(2-pyridylthio)propenamide];
10 *N*-(1-Aza-bicyclo[2.2.2]oct-3-yl)[E-3-(2-pyridylthio)propenamide];
N-(1-Aza-bicyclo[2.2.2]oct-3-yl)[Z-3-(4-pyridylthio)propenamide];
N-(1-Aza-bicyclo[2.2.2]oct-3-yl)[E-3-(4-pyridylthio)propenamide];
N-(1-Aza-bicyclo[2.2.2]oct-3-yl)[Z-3-(2-pyrimidinylthio)propenamide];
N-(1-Aza-bicyclo[2.2.2]oct-3-yl)[E-3-(2-pyrimidinylthio)propenamide];
15 *N*-(1-Aza-bicyclo[2.2.2]oct-3-yl)[Z-3-(2-methyl-3-furanylthio)propenamide];
N-(1-Aza-bicyclo[2.2.2]oct-3-yl)[E-3-(2-methyl-3-furanylthio)propenamide];
N-(1-Aza-bicyclo[2.2.2]oct-3-yl)[E-3-(2-imidazolylthio)propenamide];
N-(1-Aza-bicyclo[2.2.2]oct-3-yl)[Z-3-(phenylthio)-3-(methyl)propenamide];
N-(1-Aza-bicyclo[2.2.2]oct-3-yl)[Z-3-(2-benzothiazolylthio)propenamide];
20 *N*-(1-Aza-bicyclo[2.2.2]oct-3-yl)[E-3-(2-benzothiazolylthio)propenamide];
N-(1-Aza-bicyclo[2.2.2]oct-3-yl)[Z-3-(1-methyl-2-imidazolylthio)propenamide];
N-(1-Aza-bicyclo[2.2.2]oct-3-yl)[E-3-(1-methyl-2-imidazolylthio)propenamide];
N-(1-Aza-bicyclo[2.2.2]oct-3-yl)[Z-3-(5-methyl-1,3,4-thiadiazol-2-
ylthio)propenamide];
25 *N*-(1-Aza-bicyclo[2.2.2]oct-3-yl)[E-3-(5-methyl-1,3,4-thiadiazol-2-
ylthio)propenamide];
N-(1-Aza-bicyclo[2.2.2]oct-3-yl)[Z-3-(4-chlorophenylthio)propenamide];
N-(1-Aza-bicyclo[2.2.2]oct-3-yl)[Z-3-(2-thiazolylthio)propenamide];
N-(1-Aza-bicyclo[2.2.2]oct-3-yl)[Z-3-(2-thienylthio)propenamide];
30 *N*-(1-Aza-bicyclo[2.2.2]oct-3-yl)[E-3-(2-thienylthio)propenamide];
N-(1-Aza-bicyclo[2.2.2]oct-3-yl)[Z-3-(2-benzoxazolylthio)propenamide];
N-(1-Aza-bicyclo[2.2.2]oct-3-yl)[E-3-(2-benzoxazolylthio)propenamide];

N-(1-Aza-bicyclo[2.2.2]oct-3-yl)[Z-3-(4-trifluoromethyl-2-pyrimidinylthio)propenamide];

N-(1-Aza-bicyclo[2.2.2]oct-3-yl)[Z-3-(4-fluorophenylthio)propenamide];

N-(1-Aza-bicyclo[2.2.2]oct-3-yl)[E-3-(4-fluorophenylthio)propenamide];

5 *N*-(1-Aza-bicyclo[2.2.2]oct-3-yl)[Z-3-(2-thiazolo[4,5-b]pyridylthio)propenamide];

(*R*)-*N*-(1-Aza-bicyclo[2.2.2]oct-3-yl)[E-3-(2-thiazolo[4,5-b]pyridylthio)propenamide];

N-(1-Aza-bicyclo[2.2.2]oct-3-yl)[Z-3-(3-fluorophenylthio)propenamide];

N-(1-Aza-bicyclo[2.2.2]oct-3-yl)[E-3-(3-fluorophenylthio)propenamide];

or an enantiomer thereof, and the pharmaceutically acceptable salts thereof.

10

8. A compound according to claim 1, said compound being:

(*R*)-*N*-(1-Aza-bicyclo[2.2.2]oct-3-yl)[Z-3-(phenylthio)propenamide] hydrochloride;

(*R*)-*N*-(1-Aza-bicyclo[2.2.2]oct-3-yl)[Z-3-(4-methylphenylthio)propenamide];

(*R*)-*N*-(1-Aza-bicyclo[2.2.2]oct-3-yl)[E-3-(4-methylphenylthio)propenamide];

15 (*R*)-*N*-(1-Aza-bicyclo[2.2.2]oct-3-yl)[Z-3-(3-methylphenylthio)propenamide];

(*R*)-*N*-(1-Aza-bicyclo[2.2.2]oct-3-yl)[E-3-(3-methylphenylthio)propenamide];

(*R*)-*N*-(1-Aza-bicyclo[2.2.2]oct-3-yl)[Z-3-(2-methylphenylthio)propenamide];

(*R*)-*N*-(1-Aza-bicyclo[2.2.2]oct-3-yl)[E-3-(2-methylphenylthio)propenamide];

(*R*)-*N*-(1-Aza-bicyclo[2.2.2]oct-3-yl)[Z-3-(4-methoxyphenylthio)propenamide];

20 (*R*)-*N*-(1-Aza-bicyclo[2.2.2]oct-3-yl)[E-3-(4-methoxyphenylthio)propenamide];

(*R*)-*N*-(1-Aza-bicyclo[2.2.2]oct-3-yl)[Z-3-(3-methoxyphenylthio)propenamide];

(*R*)-*N*-(1-Aza-bicyclo[2.2.2]oct-3-yl)[E-3-(3-methoxyphenylthio)propenamide];

(*R*)-*N*-(1-Aza-bicyclo[2.2.2]oct-3-yl)[Z-3-(2-methoxyphenylthio)propenamide];

(*R*)-*N*-(1-Aza-bicyclo[2.2.2]oct-3-yl)[E-3-(2-methoxyphenylthio)propenamide];

25 (*R*)-*N*-(1-Aza-bicyclo[2.2.2]oct-3-yl)[Z-3-(2-pyridylthio)propenamide];

(*R*)-*N*-(1-Aza-bicyclo[2.2.2]oct-3-yl)[E-3-(2-pyridylthio)propenamide];

(*R*)-*N*-(1-Aza-bicyclo[2.2.2]oct-3-yl)[Z-3-(4-pyridylthio)propenamide];

(*R*)-*N*-(1-Aza-bicyclo[2.2.2]oct-3-yl)[E-3-(4-pyridylthio)propenamide];

(*R*)-*N*-(1-Aza-bicyclo[2.2.2]oct-3-yl)[Z-3-(2-pyrimidinylthio)propenamide];

30 (*R*)-*N*-(1-Aza-bicyclo[2.2.2]oct-3-yl)[E-3-(2-pyrimidinylthio)propenamide];

(*R*)-*N*-(1-Aza-bicyclo[2.2.2]oct-3-yl)[Z-3-(2-methyl-3-furanylthio)propenamide];

(*R*)-*N*-(1-Aza-bicyclo[2.2.2]oct-3-yl)[E-3-(2-methyl-3-furanylthio)propenamide];

- (*R*)-*N*-(1-Aza-bicyclo[2.2.2]oct-3-yl)[E-3-(2-imidazolylthio)propenamide];
(*R*)-*N*-(1-Aza-bicyclo[2.2.2]oct-3-yl)[Z-3-(phenylthio)-3-(methyl)propenamide];
(*R*)-*N*-(1-Aza-bicyclo[2.2.2]oct-3-yl)[Z-3-(2-benzothiazolylthio)propenamide];
(*R*)-*N*-(1-Aza-bicyclo[2.2.2]oct-3-yl)[E-3-(2-benzothiazolylthio)propenamide];
5 (*R*)-*N*-(1-Aza-bicyclo[2.2.2]oct-3-yl)[Z-3-(1-methyl-2-imidazolylthio)propenamide];
(*R*)-*N*-(1-Aza-bicyclo[2.2.2]oct-3-yl)[E-3-(1-methyl-2-imidazolylthio)propenamide];
(*R*)-*N*-(1-Aza-bicyclo[2.2.2]oct-3-yl)[Z-3-(5-methyl-1,3,4-thiadiazol-2-ylthio)propenamide];
(*R*)-*N*-(1-Aza-bicyclo[2.2.2]oct-3-yl)[E-3-(5-methyl-1,3,4-thiadiazol-2-ylthio)propenamide];
10 (*R*)-*N*-(1-Aza-bicyclo[2.2.2]oct-3-yl)[Z-3-(4-chlorophenylthio)propenamide];
(*R*)-*N*-(1-Aza-bicyclo[2.2.2]oct-3-yl)[Z-3-(2-thiazolylthio)propenamide];
(*R*)-*N*-(1-Aza-bicyclo[2.2.2]oct-3-yl)[Z-3-(2-thienylthio)propenamide];
(*R*)-*N*-(1-Aza-bicyclo[2.2.2]oct-3-yl)[E-3-(2-thienylthio)propenamide];
15 (*R*)-*N*-(1-Aza-bicyclo[2.2.2]oct-3-yl)[Z-3-(2-benzoxazolylthio)propenamide];
(*R*)-*N*-(1-Aza-bicyclo[2.2.2]oct-3-yl)[E-3-(2-benzoxazolylthio)propenamide];
(*R*)-*N*-(1-Aza-bicyclo[2.2.2]oct-3-yl)[Z-3-(4-trifluoromethyl-2-pyrimidinylthio)propenamide];
(*R*)-*N*-(1-Aza-bicyclo[2.2.2]oct-3-yl)[Z-3-(4-fluorophenylthio)propenamide];
20 (*R*)-*N*-(1-Aza-bicyclo[2.2.2]oct-3-yl)[E-3-(4-fluorophenylthio)propenamide];
(*R*)-*N*-(1-Aza-bicyclo[2.2.2]oct-3-yl)[Z-3-(2-thiazolo[4,5-b]pyridylthio)propenamide];
(*R*)-*N*-(1-Aza-bicyclo[2.2.2]oct-3-yl)[E-3-(2-thiazolo[4,5-b]pyridylthio)propenamide];
(*R*)-*N*-(1-Aza-bicyclo[2.2.2]oct-3-yl)[Z-3-(3-fluorophenylthio)propenamide];
(*R*)-*N*-(1-Aza-bicyclo[2.2.2]oct-3-yl)[E-3-(3-fluorophenylthio)propenamide];
25 or an enantiomer thereof, and the pharmaceutically acceptable salts thereof.

9. A compound according to claim 1, said compound being:

- (*R*)-*N*-(1-Aza-bicyclo[2.2.2]oct-3-yl)[Z-3-(2-pyridylthio)propenamide];
(*R*)-*N*-(1-Aza-bicyclo[2.2.2]oct-3-yl)[E-3-(2-pyridylthio)propenamide];
30 (*R*)-*N*-(1-Aza-bicyclo[2.2.2]oct-3-yl)[Z-3-(2-pyrimidinylthio)propenamide];
or an enantiomer thereof, and the pharmaceutically acceptable salts thereof.

10. A compound according to any one of claims 1 to 9 for use in therapy.
11. A pharmaceutical composition including a compound as defined in any one of claims 1 to 9, in admixture with an inert pharmaceutically acceptable diluent or carrier.
- 5 12. The pharmaceutical composition according to claim 11, for use in the treatment or prophylaxis of psychotic disorders or intellectual impairment disorders.
13. The pharmaceutical composition according to claim 11, for use in the treatment or
10 prophylaxis of human diseases or conditions in which activation of the $\alpha 7$ nicotinic receptor is beneficial.
14. The pharmaceutical composition according to claim 11 for use in the treatment or prophylaxis of Alzheimer's disease, learning deficit, cognition deficit, attention deficit,
15 memory loss, Attention Deficit Hyperactivity Disorder, Lewy Body Dementia, anxiety, schizophrenia, or mania or manic depression, Parkinson's disease, Huntington's disease, Tourette's syndrome, neurodegenerative disorders in which there is loss of cholinergic synapse, jetlag, cessation of smoking, nicotine addiction including that resulting from exposure to products containing nicotine, pain, or ulcerative colitis.
- 20 15. The pharmaceutical composition according to claim 11, for use in the treatment or prophylaxis of Alzheimer's disease, learning deficit, cognition deficit, attention deficit, Lewy Body Dementia, memory loss or Attention Deficit Hyperactivity Disorder.
- 25 16. The pharmaceutical composition according to claim 11, for use in the treatment or prophylaxis of anxiety, schizophrenia, or mania or manic depression.
17. The pharmaceutical composition according to claim 11, for use in the treatment or prophylaxis of Parkinson's disease, Huntington's disease, Tourette's syndrome, or
30 neurodegenerative disorders in which there is loss of cholinergic synapses.

18. The pharmaceutical composition according to claim 11, for use in the treatment or prophylaxis of jetlag, nicotine addiction including that resulting from exposure to products containing nicotine, pain, or ulcerative colitis.
- 5 19. The pharmaceutical composition according to claim 11, for use in the treatment or prophylaxis of Alzheimer's disease.
20. Use of a compound as defined in any one of claims 1 to 9 in the manufacture of a medicament for the treatment or prophylaxis of psychotic disorders or intellectual impairment
10 disorders.
21. The use of a compound as defined in any one of claims 1 to 9, in the manufacture of a medicament for the treatment or prophylaxis of human diseases or conditions in which activation of the $\alpha 7$ nicotinic receptor is beneficial.
- 15 22. The use of a compound as defined in any one of claims 1 to 9, in the manufacture of a medicament for the treatment or prophylaxis of Alzheimer's disease, learning deficit, cognition deficit, attention deficit, memory loss, Attention Deficit Hyperactivity Disorder, Lewy Body Dementia, anxiety, schizophrenia, or mania or manic depression, Parkinson's
20 disease, Huntington's disease, Tourette's syndrome, neurodegenerative disorders in which there is loss of cholinergic synapse, jetlag, cessation of smoking, nicotine addiction including that resulting from exposure to products containing nicotine, pain, or ulcerative colitis.
23. The use according to claim 22, wherein the condition or disorder is Alzheimer's
25 disease, learning deficit, cognition deficit, attention deficit, memory loss, Lewy Body Dementia, or Attention Deficit Hyperactivity Disorder.
24. The use according to claim 22, wherein the disorder is anxiety, schizophrenia, or mania or manic depression.

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25. The use according to claim 22, wherein the disorder is Parkinson's disease, Huntington's disease, Tourette's syndrome, or neurodegenerative disorders in which there is loss of cholinergic synapses.

5 26. The use according to claim 22, wherein the condition or disorder is Alzheimer's disease.

27. The use according to claim 22, wherein the condition or disorder is jetlag, nicotine addiction including that resulting from exposure to products containing nicotine, pain, and for
10 ulcerative colitis.

28. A method of treatment or prophylaxis of psychotic disorders or intellectual impairment disorders, which comprises administering a therapeutically effective amount of a compound as defined in any one of claims 1 to 9.

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29. A method of treatment or prophylaxis of human diseases or conditions in which activation of the $\alpha 7$ nicotinic receptor is beneficial which comprises administering a therapeutically effective amount of a compound as defined in any one of claims 1 to 9.

20 30. The method according to claim 28 or claim 29, wherein the disorder is Alzheimer's disease, learning deficit, cognition deficit, attention deficit, memory loss. Attention Deficit Hyperactivity Disorder, Lewy Body Dementia, anxiety, schizophrenia, mania or manic depression, Parkinson's disease, Huntington's disease, Tourette's syndrome, neurodegenerative disorders in which there is loss of cholinergic synapse. jetlag, cessation of
25 smoking, nicotine addiction including that resulting from exposure to products containing nicotine, pain, or ulcerative colitis.

31. The method according to claim 28 or claim 29, wherein the disorder is Alzheimer's disease, learning deficit, cognition deficit, attention deficit, memory loss, Lewy Body
30 Dementia, or Attention Deficit Hyperactivity Disorder.

32. The method according to claim 28 or claim 29, wherein the disorder is Parkinson's disease, Huntington's disease, Tourette's syndrome, or neurodegenerative disorders in which there is loss of cholinergic synapses.
- 5 33. The method according to claim 28 or claim 29, wherein the disorder is anxiety, schizophrenia or mania or manic depression.
34. The method according to claim 28 or claim 29, wherein the disorder is jetlag, nicotine addiction, pain, and for ulcerative colitis.
- 10 35. The method according to claim 28 or claim 29, wherein the disorder is Alzheimer's disease.

INTERNATIONAL SEARCH REPORT

International application No.

PCT/SE 00/01993

A. CLASSIFICATION OF SUBJECT MATTER

IPC7: C07D 453/02, C07D 451/04, A61K 31/439, A61K 31/46, A61P 25/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC7: C07D, A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

SE,DK,FI,NO classes as above

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 9420465 A1 (GLAXO S.P.A.), 15 Sept 1994 (15.09.94), see claims and page 5, lines 14-32 --	1-12,14-20, 22-28,30-35
X	STN International, File CAPLUS, CAPLUS accession no. 1995:904880, Document no. 124:649, Kostochka, L.M. et al: "Synthesis and local -anesthetic activity of tropane enamides and amides"; & Khim.-Farm. Zh. (1995), 29(3), 40-2 --	1-11,14,18, 22,27,30,34
A	WO 9801443 A1 (SMITHKLINE BEECHAM S.P.A. ET AL), 15 January 1998 (15.01.98) --	1-35

☒ Further documents are listed in the continuation of Box C.☒ See patent family annex.

* Special categories of cited documents:

- "A" document defining the general state of the art which is not considered to be of particular relevance
- "E" earlier application or patent but published on or after the international filing date
- "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- "O" document referring to an oral disclosure, use, exhibition or other means
- "P" document published prior to the international filing date but later than the priority date claimed

"I" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance: the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance: the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search

26 January 2001

Date of mailing of the international search report

02-02-2001

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INTERNATIONAL SEARCH REPORT

International application No.

PCT/SE 00/01993

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 9621644 A1 (SMITHKLINE BEECHAM S.P.A.), 18 July 1996 (18.07.96) --	1-35
A	EP 0581165 A2 (DOMPE' FARMACEUTICI S.P.A.), 2 February 1994 (02.02.94) -- -----	1-35

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE 00/01993**Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)**

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.: **28-35**
because they relate to subject matter not required to be searched by this Authority, namely:
see next sheet
2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

27/12/00

International application No.

PCT/SE 00/01993

Patent document cited in search report.			Publication date	Patent family member(s)		Publication date
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				ZA	9401483 A	11/11/94
WO	9801443	A1	15/01/98	AU	3620597 A	02/02/98
				BR	9710230 A	10/08/99
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				CZ	9900037 A	11/08/99
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				GB	9614367 D	00/00/00
				IL	127668 D	00/00/00
				JP	2000514074 T	24/10/00
				NO	990080 A	08/01/99
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				ZA	9706064 A	08/02/99
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				GB	9626700 D	00/00/00
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WO	9621644	A1	18/07/96	AP	648 A	25/05/98
				AP	9701029 D	00/00/00
				AU	4536096 A	31/07/96
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				CZ	9702176 A	18/03/98
				EP	0802902 A	29/10/97
				FI	972919 A	09/09/97
				HU	9901096 A	28/07/99
				IT	1272878 B	01/07/97
				IT	MI950030 A,U,V	10/07/96
				JP	10512251 T	24/11/98
				NO	973178 A	09/09/97
				PL	321263 A	24/11/97
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